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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,337	02/12/2004	Changquan Sun	PC28117A	1777

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EXAMINER	
FREISTEIN, ANDREW B	
ART UNIT	**PAPER NUMBER**
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,337	SUN ET AL.	
	Examiner	Art Unit	
	Andrew B. Freistein	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *19-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/12/04 & 2/2/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 12/07/2006 was entered. Claims 1-28 are pending.

Priority

This application claims benefit of US Provisional Application No. 60/448,863, filed 02/24/2003.

Information Disclosure Statement

Applicant's information disclosure statements (IDS), filed on 8/12/2004 and 2/2/2005, have been considered. Please refer to Applicant's copies of the 1449 submitted herewith.

Restriction Requirement

In a response filed 12/07/2006, Applicant elected (with traverse) Group II, claims 2, 4-8, 13-14, 16 and 18, drawn to compounds of formula I.

Applicant traverses the restriction requirement asserting that there is no search burden. Because Group I and Group II are each drawn to a compound of formula I, Group I and Group II are rejoined. Thus, claims 1-18 are the elected claims currently under examination (product claims).

Group III remains withdrawn subject matter. Group III is drawn to a method of using a compound of formula I, which is classified in class 514, subclass 414. Furthermore, newly formed Group I and Group III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially

different process of using that product (MPEP § 806.05(h)). In the instant case the process of treating leukemia can be practiced with a materially different product (see US Pat. No. 6,333,333, col. 161, claim 9). As a result, the restriction requirement between the product claims and the method of use claims is maintained and made FINAL.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Lipson et al., US 2002/0010203.

Claim 1 is drawn to a compound of formula I substantially free of polymorph I. Claim 2 is drawn to a compound of formula I substantially free of polymorph II. Claim 18 is drawn to pharmaceutical composition comprising a compound of formula I substantially free of polymorph II. The compound of formula I is: 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-ylethyl)-amide.

Lipson et al. disclose using the compound 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-ylethyl)-amide for inhibiting cell proliferative disorders (see p. 6, paragraph [0075], and p. 21, compound XVII).

Additionally, Lipson et al. disclose pharmaceutical compositions comprising the compound (see p. 13, paragraph [0149] - p. 15, paragraph [0183]).

The claim limitation "substantially free of polymorph I [or II]" has no patentable weight, because the claim is drawn to "a compound." As a result the disclosure of the compound anticipates claims 1 and 2.

Please note that one category of patentable invention is a "product." A novel or unobvious chemical product is identified first by its "chemical nature," i.e. elemental content an their ratios. It is well known in the pharmaceutical art that drugs are known to have polymorphic forms (see US pharmacopia #23, national formulary #18 (1995). It is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice. Thus, *in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules* (see Polymorphism in Pharmaceutical Solids (1999), Brittain p. 1-2). Therefore, for a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis for an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hydroscopicity, recovery, prevention of precipitation, etc.

The instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it is recognized in the pharmaceutical field, many solids exhibit polymorphism, which is the innate nature of the particular drug. There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existed different "morph" will display different physical properties such as X-ray diffraction pattern, melting point, etc. Simply because it is "different" does

not merit the new from patentable. Moreover, according to one of ordinary skill in the art (Brittain) products that merely differ in the form of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. (see Brittain, p. 1-2, In re Cofer 148 USPQ 268, and Ex parte Hartop, 139 USPQ 525).

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-17 are rejected under 35 U.S.C. 103(a) as being obvious over Tang et al., US 6,573,293.

The applied reference has a common inventor (Michael Hawley) with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 3 and 4 are drawn to compounds of formula I with a powder X-ray diffraction spectrum. Each claim is drawn to a different polymorph with a set of 5 peaks.

Claims 5-8 are drawn to a composition comprising polymorph I of a compound of formula I.

Claims 9-12 are drawn to a composition comprising polymorph II of a compound of formula I.

Claims 13-17 are drawn to a polymorph made by a specific process (i.e. a product by process claim).

Determining the Scope and Content of the Prior Art

Tang et al. disclose the process of producing the compound 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-ylethyl)-amide as an orange solid and the scale-up procedure (see col. 211, example 129). The H-NMR data is provided for both the original and the scaled-up product. Additionally, Tang et al. disclose pharmaceutical compositions comprising the compound (see col. 170, line 40 – col. 177).

Ascertaining the Differences Between the Instant Application and the Prior Art

The instant invention is drawn to polymorph forms I and II of the compound 5-[5-Fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl]-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-pyrrolidin-1-ylethyl)-amide and pharmaceutical compositions comprising the polymorph. On the other hand, the prior art discloses the compound in a crude product form and does specifically identify the polymorph.

Finding Prima Facie Obviousness

It has long been the practice in the chemical and pharmaceutical arts to produce compounds in the form of crystals to secure a pure product. There is no patentable distinction in the concept of a chemical compound in crystalline form over the same compound in its amorphous form. *In re Weijlard*, 69 U.S.P.Q. 86, 87 (C.C.P.A. 1946).

Changing the form, purity, color, or other characteristic of an old product without a new use as a result thereof does not render product patentable where utility remains the same. *Ex parte Hartop*, 139 USPQ 525. Therefore, absent a showing of a viable

unexpected, unobvious and superior properties, the instant claimed compound would have been suggested to one skilled in the art.

Further, changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art. *In re Cofer*, 148 U.S.P.Q. 268 (CCPA 1966). Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art. Additionally, since Applicant(s) are claiming a similar method of using the crystalline forms to that of the amorphous form, a showing of unobvious and superior properties in using the crystalline form for this similar method of use would also have to shown.

One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc. Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline forms of known compounds would have been suggested to one skilled in the art.

The compounds are of the same identical formula and as such would be expected to have the same utility. The difference, if any, may reside in there being different crystalline forms. One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g.

improved solubility, shelf-life, improved mode of administering properties, etc. In the absence of a showing of a viable unexpected property (not just a difference in X-ray crystallography), the instant claimed invention is found obvious.

Furthermore, with respect to claims 13-17, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (see MPEP 2113).

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

(1) Claims 3 and 4 are drawn to compounds of formula I with a powder X-ray diffraction spectrum. Each claim is drawn to a different polymorph with a set of 5 peaks.

However, the data provided in Claims 3 and 4 is not sufficient to distinguish the polymorph forms I and II from the compound and other polymorphs.

According to Polymorphism in Pharmaceutical Solids:

> The USP general chapter on x-ray diffraction states that identity is established if the scattering angles of the ten strongest reflections obtained for an analyte agree to within ±0.20 degrees with that of the reference material, and if the relative intensities of these reflections do not vary by more than 20 percent (see Brittain, p. 236).

In this case, claims 3 and 4 shows XRPD data that does not meet the standard practice and it fails to properly characterize the claimed polymorph. As a result, claims 3 and 4 do not enable one of ordinary skill in the art to make and use the polymorph.

(2) Claims 5-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the formulation of a pharmaceutical composition, maintaining a polymorph is not automatic. Some polymorphs are more difficult to formulate than others because of their shape or hygroscopicity and the tablet can loose its bioavailablity (see Rouhi, "The Right Stuff," Chem. & Engineering News (2003), p. 33, col. 2). The specification of the instant application fails to describe how the polymorph of claim 1 will be maintained in a pharmaceutical composition. Consequently, Claims 5-12 are rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, the limitation "substantially free of polymorph I form" is indefinite. It fails to provide the meets and bounds of the claims. One of ordinary skill in the art does not know what else the compound can have in it. Rather, all ne of ordinary skill in the art does not knows is what the compound is "substantially" free of.

Similarly, claim 2 has the limitation, "substantially free of polymorph II form," which is indefinite for the same reasons as claim 1.

Claims 3 and 4 are indefinite, because they fail to meet the minimum standard in the art for a powder X-ray diffraction pattern (see 35 USC § 112, 1st Paragraph above) and because it fails to provide and alternative method of distinguishing the claimed polymorph over the others. In order to overcome this rejection, claims 3 and 4 must provide, along with the minimum standard in the art for a powder X-ray diffraction pattern, either a melting point, IR spectroscopy data, H-NMR spectroscopy data, or differential scanning calorimetry (DSC) data.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew B. Freistein whose telephone number is (571) 272-8515. The examiner can normally be reached Monday-Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

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Date: January 12, 2007